Tetrahedron Letters 51 (2010) 2115–2118

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple and selective method for the *O*-AcCl removal using sodium borohydride

Emmanuelle Villedieu, Chrystel Lopin-Bon, Sabine Berteina-Raboin *

Institut de Chimie Organique et Analytique, Université d'Orléans, UMR CNRS 6005, BP 6759, 45067 Orléans Cedex 2, France

ARTICLE INFO

Article history:
Received 3 December 2009
Revised 5 February 2010
Accepted 10 February 2010
Available online 18 February 2010

ABSTRACT

A deprotection of chloroacetylated alcohols using $NaBH_4$ is reported. The free alcohols are obtained in excellent yields. The reaction was performed on primary, secondary, alkyl, allyl, benzylic alcohols and phenols. The compatibility of the method with other sensitive or protective groups is demonstrated.

1. Introduction

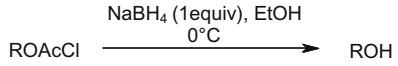
The chloroacetyl (AcCl) is an important group for the synthesis of various compounds and is commonly used in carbohydrate chemistry. This protecting group is used for the temporary protection of hydroxyl groups, as it is a very base-sensitive group due to the inductive effect of the chlorine substituent and can be selectively removed in the presence of other acyl functions by a number of methods,[1] mainly using a nucleophilic attack. In addition to aqueous ammonia,[2] hydrazine acetate,[3] hydrazine dithiocarbonate (HDTC)[4], or 1-selenocarbamoylpiperidine[5] for example, the most widely used deprotection reagent is thiourea.[6] Deprotections using tertiary amine as a base were reported too.[7] The latter reactions allow the presence of other protecting groups but require either relatively long reaction times and/or high temperature, or preparation of the reagent just before use,[8] or large excess of reagents which cannot be compatible to sensitive compounds.

2. Results and discussion

In addition to the existing methods for deprotecting the *O*-AcCl group, we propose an alternative to deprotect AcCl under soft conditions. Sodium borohydride ($NaBH_4$) turned out to be selective, fast and easy to handle (Scheme 1). The reaction provides the corresponding alcohol in very good yields and can be performed at low temperatures.

The *O*-AcCl deprotection was performed using chloroacetylgeraniol as a typical example.[9]

The scope and limitation of the method were investigated on various primary, secondary, alkyl, allyl, benzylic alcohols and phenols (Table 1). In most cases, the treatment of *O*-AcCl-protected alcohols with 1 equiv $NaBH_4$ in EtOH at low temperature gave the corresponding deprotected alcohols in excellent 71–95% yield. Sensitive compounds such as epoxides or sugars were deprotected in the same way, in very good yields.



Scheme 1. General scheme for the $NaBH_4$ cleavage of *O*-AcCl protective groups.

The orthogonality of the deprotection was then examinated (Table 2) and structures bearing other protective groups such as acyl groups (entries 1, 2 and 3), silylethers (entries 4 and 5) or other kinds (entries 6 and 7) were treated. It appeared that no other groups were affected.

Continuing this investigation, it was noticed that an equimolar amount of hydride (0.25 equiv of $NaBH_4$) allowed the deprotection of **1** to **1a** in 73% yield (Scheme 2).

It is noteworthy to mention that the selectivity of the *O*-AcCl deprotection by $NaBH_4$ was also studied using compound **7** which bears both aromatic and alkyl *O*-AcCl protection. The reaction was performed with 0.25 equiv of $NaBH_4$ in EtOH at 0 °C. Under these conditions, only the cleavage of the protected phenol was observed in 84% yields (Scheme 3). The structure of **7b** was established by the comparison between ^1H NMR, ^{13}C NMR of **7**, **7a** and **7b** (see analytical data of **7**, **7a** and **7b**).[10–12] Particularly, we observed in ^1H NMR spectrum of **7b**, recorded in $CDCl_3$, the disappearance of a singlet at 4.29 ppm (corresponding to the chloromethyl–CH_2Cl) and the appearance of a broad signal at 5.93 ppm corresponding to the OH, the shifts of CH_2 groups did not change.

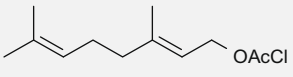
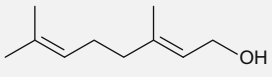
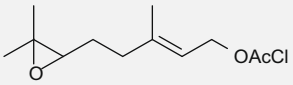
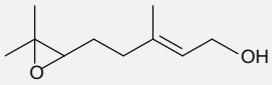
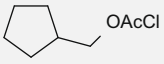
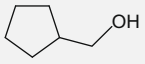
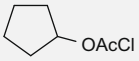
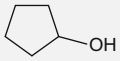
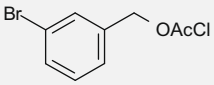
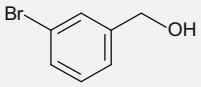
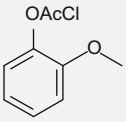
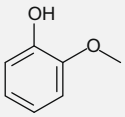
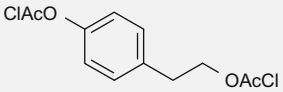
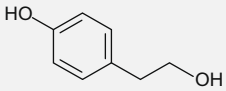
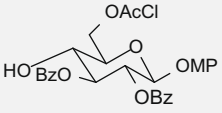
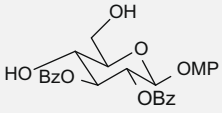
As we observed the selectivity of deprotection of phenolic over alkyl *O*-AcCl, we decided to study it for other combinations (Schemes 4 and 5).

It appeared that the selective cleavage of phenolic esters over homobenzyl (Scheme 3) or benzyl esters (Scheme 4) was possible.

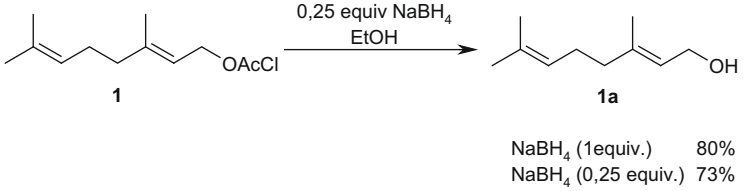
* Corresponding author. Tel.: +33 2 38 49 48 56; fax: +33 2 38 41 72 81.
E-mail address: sabine.berteina-raboin@univ-orleans.fr (S. Berteina-Raboin).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.057

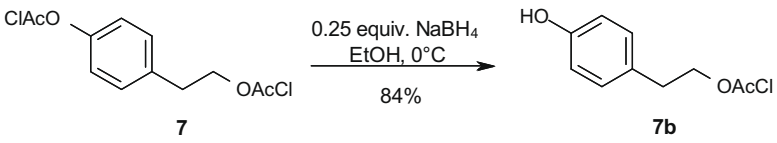
Table 1
Cleavage of the *O*-AcCl-protected compounds with $NaBH_4$

Entry	Substrate	Product	Yield[a] (%)
1	 **1**	 **1a**	80
2	 **2**	 **2a**	79
3	 **3**	 **3a**	95
4	 **4**	 **4a**	95
5	 **5**	 **5a**	96
6	 **6**	 **6a**	96
7	 **7**	 **7a**	81
8	 **8**	 **8a**	86

[a] Yields are given in isolated products after short column chromatography, all compounds were either compared with known data in the literature or if new, fully characterized by IR, ^1H NMR, ^{13}C NMR and MS.



Scheme 2. Results of $NaBH_4$ cleavage of **1**.

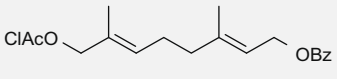
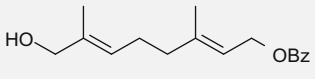
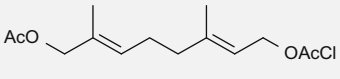
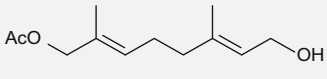
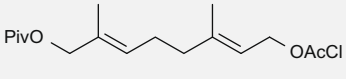
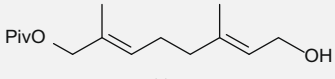
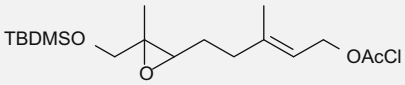
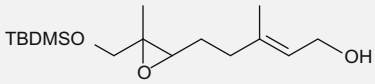
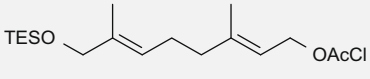
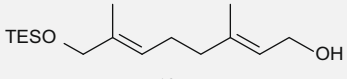
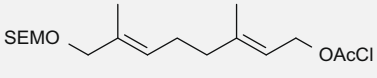
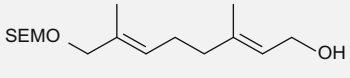
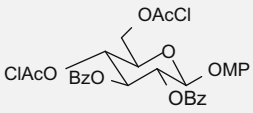
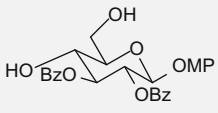


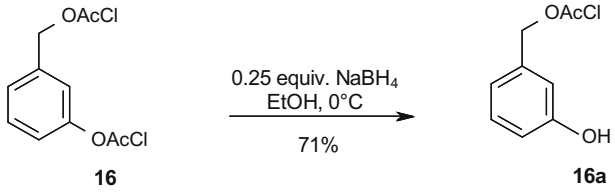
Scheme 3. Result of $NaBH_4$ selective cleavage of **7**.

Unfortunately, no selectivity was observed for the cleavage of primary over secondary protected alcohols.

In order to conclude on the investigations on this new method of *O*-AcCl cleavage, we intended to deprotect compounds bearing both protected alcohol and carbonyl group. The treatment of compound **18** with 0.25 equiv of $NaBH_4$ did not lead to any selectivity, but to a mixture of deprotection and/or reduction (Scheme 6).

Table 2
Studies on the orthogonality of the cleavage of the *O*-AcCl-protected compounds with $NaBH_4$

Entry	Substrate	Product	Yield (%)
1	 **9**	 **9a**	75
2	 **10**	 **10a**	93
3	 **11**	 **11a**	80
4	 **12**	 **12a**	78
5	 **13**	 **13a**	91
6	 **14**	 **14a**	81
7	 **15**	 **15a**	71

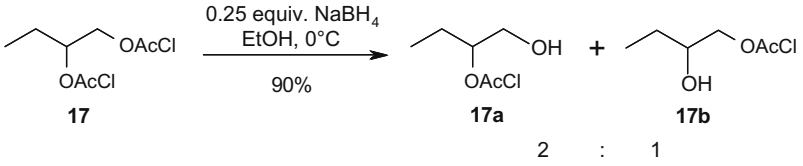


16 **16a**

Scheme 4. Result of $NaBH_4$ selective cleavage of **16**.

3. Conclusion

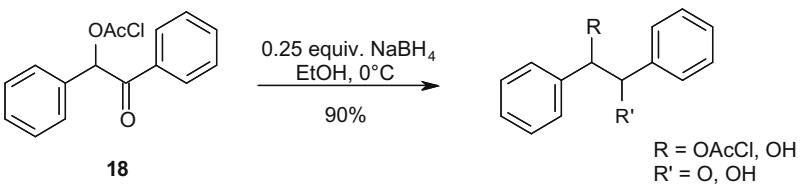
To conclude, we found a simple and selective method for the cleavage of AcCl-protected alcohols using $NaBH_4$. The reaction conditions are compatible with other protective and sensitive groups. Moreover, the protected group was removed at low temperature, in short time, and was compatible with sensitive starting materials and the procedure was easy to perform. The method was used to deprotect aromatic and phenolic *O*-AcCl over alkyl ones. No selectivity was observed for primary over secondary protected alcohols.



17 **17a** **17b**

2 : 1

Scheme 5. Result of $NaBH_4$ non-selective cleavage of **17**.



18

Scheme 6. Result of $NaBH_4$ non-selective cleavage of **18**.

Unfortunately, it was not possible to cleave AcCl in the presence of a carbonyl group without leading to the reduction.

References and notes

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, 1999. and references cited therein; Goering, B. K. Ph.D. Dissertation, Cornell University, 1995.
2. Reese, C. B.; Stewart, J. C. M.; Van Boom, J. H.; de Leeuw, H. P. M.; Nagel, L.; de Rooy, J. F. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 934–942; Buchanan, J. G.; Sable, H. Z.. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley: New York, 1972; Vol. 2, pp 1–95.
3. Udodong, U. E.; Rao, C. S.; Fraser-Reid, B. *Tetrahedron* **1992**, *48*, 4713–4724.
4. Van Boeckel, C. A. A.; Beetz, T. *Tetrahedron Lett.* **1983**, *24*, 3775–3778.
5. Sogabe, S.; Ando, H.; Koketsu, M.; Ishihara, H. *Tetrahedron Lett.* **2006**, *47*, 6603–6606.
6. Blatter, G.; Jacquinet, J. C. *Carbohydr. Res.* **1996**, *288*, 109–125.
7. Kanie, O.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1996**, *37*, 4551–4554; Lefeber, D. J.; Kamerling, J. P.; Vliegenthart, J. F. G. *Org. Lett.* **2000**, *2*, 701–703.
8. Smith, A. B., III; Hale, K. J.; Vaccaro, H. A.; Rivero, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 2112–2122.
9. $NaBH_4$ (1 equiv) was added to a stirred solution of chloroacetylgeraniol (1 equiv) in EtOH under argon at 0 °C and the reaction mixture was stirred at room temperature for 30 min. Addition of iced water followed by three extractions with CH_2Cl_2 gave an organic layer which was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford expected geraniol in 80% yield.
10. Typical experiment protocol of chloroacetylation: Chloroacetic anhydride (1 equiv/OH) was added to a stirred solution of commercially available 4-hydroxyphenethyl alcohol in a mixture of pyridine/CH_2Cl_2 (1:3) (4 mL/mmol) under argon at room temperature. After 2 h, addition of ice water followed by three extractions with CH_2Cl_2 gave an organic solution which was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was subjected to a short column chromatography on silica gel to afford the corresponding protected compound **7** in 76% yields. Analytical data for **7** are as follows. 4-[2-(2-chloroacetyl)oxyethyl]phenyl-2-chloroacetate. ^{1}H NMR (250 MHz, *CDCl*$_3$): δ 7.25 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.08 (2H, d, *J* = 8.5 Hz, Ar*H*), 4.39 (2H, t, *J* = 7.0 Hz, C*H*$_2$O), 4.29, 4.05 (2 × 2H, 2s, 2C*H*$_2$Cl), 2.98 (2H, t, *J* = 7.0 Hz, PhC*H*$_2$). ^{13}C NMR (62.5 MHz, *CDCl*$_3$): δ 167.4 (CO), 166.1 (CO), 149.3 (C), 135.6 (C), 130.2 (CH), 121.4 (CH), 66.5 (C*H*$_2$O), 41.1 (*C*H$_2$Cl), 41.0 (*C*H$_2$Cl), 34.6 (Ph*C*H$_2$). IR (diamand ATR): 2958, 1744, 1131 (cm^{-1}). MS (IS) 308, 310, 313, 315 $(M+18)^+$.
11. Compound **7a** is obtained from **7** as described for **1a** using 1 equiv of $NaBH_4$. Analytical data for **7a** were in agreement with the literature: The Aldrich Library of ^{13}C and ^{1}H NMR Spectra, 1st ed., Vol II; Aldrich, 1993.
12. Compound **7b** is obtained from **7** as described for **1a** using 0.25 equiv of $NaBH_4$. Analytical data for **7b** are as follows. 2-(4-Hydroxyphenyl)ethyl-2-chloroacetate. RMN ^{1}H (250 MHz, *CDCl*$_3$): δ 6.98 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.70 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.93 (1H, br s, OH), 4.27 (2H, t, *J* = 7.0 Hz, C*H*$_2$O), 3.97 (2H, s, C*H*$_2$Cl), 2.81 (2H, t, *J* = 7.0 Hz, PhC*H*$_2$). RMN ^{13}C (62.5 MHz, *CDCl*$_3$): δ 167.4 (CO), 154.4 (C), 130.0 (CH), 129.5 (C), 115.4 (CH), 66.8 (C*H*$_2$O), 40.8 (*C*H$_2$Cl), 34.0 (Ph*C*H$_2$). IR (diamand ATR): 2965, 1745, 1129 (cm^{-1}). MS (IS) 237, 239 $(M+23)^+$.